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09/868,569	01/22/2002	Enno Christophers	33808F150	1492

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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/868,569	CHRISTOPHERS ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4,7-12,15,16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,13,14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/01 and 3/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1 The petition under 37 CFR 1.137(b), filed October 25, 2004, to revive the above-identified application is GRANTED and the copy of the same is mailed to the applicant 11/22/04.

2. Applicant's response to restriction and the amendment filed on 10/25/04 is entered.

Response

3. Applicant elected Group I, claims 1-6, 13, 14, 15, 17 and 18 drawn to a protein and a pharmaceutical composition and a method of using said protein with traverse.

The traversal is on the ground that the proteins etc of Group I and nucleic acids etc of Group II do not lack unity of invention if examined in the same application. The nucleic acids, after all, derive utility from the encoding of the proteins of Group I. Furthermore, the examiner has not even alleged, let alone established, any searching burden for examining the full scope of at least Group I and/or II. This full scope would include examining all eight sequences identified in the office action. It is not seen where any searching burden would be involved.

The arguments have been fully considered but found to be nonpersuasive because it is noted that the independent claim 1 is drawn to protein which does not share a common structure or function or property with DNA of group II. Further neither the mature protein or active mature protein that has allelic modifications of one of the amino acid sequences, whereby at least one amino acid of the amino acid sequence is substituted, deleted, or inserted, without in this case significantly affecting the activity of the active protein are required to or could possibly encoded by DNA as defined by PCT Rule 13.2.

Concerning the burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The protein database searches required by each of the sequences and the literature searches for each of the sequences, both of which are particularly relevant in this art, are not co-extensive and are much more important in evaluating the burden of search. Further, it is doubted that applicants would readily accept the rejection of a protein for DNA. Clearly different searches and issues are involved in the examination of each group.

It is noted that claim 15 is drawn to process of synthesizing protein should have been in group II, DNA. Claim 18 is drawn to Bandage and should have been a separate invention drawn to device. The examiner called the applicant and left a voice mail message informing the same (Attorney Anthony,7/3/07). Therefore, claims 15 and 18 are not examined along with the Group I, drawn to protein.

Status of Claims

4 Claims 1-20 are pending.

Claims 1-6, 13, 14 and 17 with respect to elected SEQ.ID.NO:1 are under examination. Since applicant elected SEQ.ID.NO:1 and claim 4 does not recite SEQ.ID.NO:1, the claim is withdrawn from the elected invention.

Claims 4, 7-12, 15, 16, 18, and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Information Disclosure Statement

5. Information Disclosure Statements filed on 9/21/01 and 3/6/03 are acknowledged and a signed copy of each is attached to this Office action.

Priority

6. This 09/868569 is a national stage entry of PCT/EP00/00776 filed on 02/01/2000

Objections

7. Claim 1 in line 3 refers SEQ ID NO:1 or 2 as Sequence Protocol number. However, these sequences are identified as sequence identification numbers. Correction is required

Claim Rejections - 35 USC 101

8. 35 U.S.C. 101 reads as Follows

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

9. Claims 1-3, 5-6, 13, 14 and17 as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed product and the product of nature.

The product "protein" as claimed, has the same characteristics as that found in nature because "protein ---- ." can be obtained from any source such as human body cells because the cells in a human body read on the claims because these cells contain protein or protein in a recombinant form (Snyder et al Molecular Genetics of Bacteria, American Society for Microbiology 1997).

The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" as taught by page [31] of specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-3, 5-6, 13, 14 and17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5-6, 13, 14 and17 are rejected as being vague and indefinite because the language protein/peptide is unclear as to whether the applicant is claiming a mature protein or peptide (protein fragment) Is this what you mean Padma?. Claims 1-3, 5-6, 13, 14 and17 are rejected as being vague and indefinite because the language protein/peptide is unclear as to whether the applicant is claiming a mature protein or peptide (protein fragment)
Generally two or more amino acids chained together by a bond called a "peptide ". Therefore, it is confusing what is being claimed in claim 1 since SEQ.ID.NO;1 does not appear to be full-length protein.
Furthermore, claim 1 recites in line 14, step (a) and (b), however, there is no step (b).
Also claim 1 is vague in reciting " activity of active protein" as what activity the claim refers to unclear.
Claim 17 provides for the use of medication for treating infections, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim17 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).
Claim 17 refers to "mixture thereof" which lacks antecedent basis. It is not clear which mixture the claim refers to since claim 1 does not recite mixture.

Claim Rejections - 35 USC 112, first paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-3, 5-6, 13, 14 and17 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.
Claims 1-3, 5-6, 13, 14 and17 are drawn to a protein /pharmaceutical composition Claim 17 can read on product too. that as an active mature protein/peptide (protein) has sequences: SEQ ID NO: 1 (Sequence Protocol No. I) (SAP-2); or that as an active mature protein has allelic modifications of one of the amino acid sequences that are mentioned above under a), whereby at least one amino acid of the amino acid sequence is substituted, deleted, or inserted, without in this case significantly affecting the activity of the active protein, or that as an active, mature protein has post-translational modifications of one of the sequences under a) and b), and said modifications do not significantly affect the activity of the active protein, said protein has an antimicrobial and/or antibiotic action, said protein has a mobility of 6 kDa in the SDS-gel electrophoresis, said protein I, protective groups are arranged at the N-terminus and/or the C-terminus and said protein is a recombinant protein. as a pharmaceutical active ingredient in the presence of pharmaceutically compatible and acceptable compounds and vehicles.

Claims 1-3, 5-6, 13, 14 and17 read broadly on widely diverse variants of SEQ ID NO:1 including the allelic modifications whereby at least one amino acid of the amino acid sequence is substituted, deleted, or inserted and post translation modifications , that have any functional alterations due to these modifications.
The state of the art teaches for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981(1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to

unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins and they differ in native conformation, binding and toxicity, thus exemplifying the importance of structural components to both biological function

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a

recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a variant product itself logically cannot adequately describe pharmaceutical comprising variant or method for producing medication using said variant of SEQ.ID.NO:!

Thus, the instant specification may provide an adequate written description of active mature protein/peptide (protein) that has sequences: SEQ ID NO: 1 (SAP-2); or that as an active mature protein has allelic modifications of one of the amino acid sequences that are mentioned above under a), whereby at least one amino acid of the amino acid sequence is substituted, deleted, or inserted, without in this case significantly affecting the activity of the active protein, or that as an active, mature protein has post-translational modifications of one of the sequences, per Lilly by structurally describing a representative number of variants of SEQ.ID.NO:1"structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an isolated protein, SEQ ID NO:1, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any variants of SEQ ID NO:1 nor does the specification provide any partial structure of variants of SEQ ID NO:1, nor any physical or chemical characteristics a variants of SEQ ID NO:,1 nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single isolated protein consisting of the amino acid sequence SEQ ID NO:1 this does not provide a description of variants of SEQ ID NO:1 that would satisfy the standard set out in Enzo.

The specification also fails to describe variants of SEQ ID NO:1 by the test set out in Lilly. The specification describes only a single protein consisting of the amino acid sequence

SEQ ID NO:1. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The prior art as shown in 102 (a) rejection under paragraph 16 , read on the presently claimed genus SEQ.ID.NO:1 that has structure associated with function. However, the claims also read on wide variety of variants of SEQ.ID.NO:1 , For example: Accession number AF473854; AAL8964 as shown below disclose a variant of SEQ.ID.NO:1 with amino acids substituted but do not appear to have antimicrobial activity. Thus the variant as claimed have no correlation between function and structure, or some combination of such characteristics."

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Qy          1 KPKGMTSSQWFKIQHMQPSPQACNSAMKNINKHTKRCKDLNTFLHEPFSSVAATCQTPKI 60
              ||| |||||||| ||:|||||||||||  |||:|:||||||||||||||||| ||||| |
Db         28 KPKDMTSSQWFKTQHVQPSPQACNSAMSIINKYTERCKDLNTFLHEPFSSVAITCQTPNI 87

Qy         61 ACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCRYKEKRQNKSYVVACKPPQKKDSQQFHLV 120
              ||||  |||||||||:|||| :|||||||||||||  |  |:||| |||: |   : ||
Db         88 ACKNSCKNCHQSHGPMSLTMGELTSGKYPNCRYKEKHLNTPYIVACDPPQQGD-PGYPLV 146

Qy        121 PVHLDRVL 128
              |||||:|:
Db        147 PVHLDKVV 154
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Thus, it appears that there should be a correlation between structure and function of the protein as evidenced by the closest prior art variant. The specification does not provide an adequate written description of variants of SEQ ID NO:1 that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed variants of SEQ ID NO:1, it also fails to adequately describe pharmaceutical composition or a method for the production of medication for treating infections comprising variants of SEQ ID NO:1.

Therefore, claims 1-3, 5-6, 13, 14 and17 do not comply with 35 USC 112, first paragraph because it is not supported by an adequate written description in the specification. Thus , these claims are also not adequately supported by an adequate written description.

14. Claims 1-3, 5-6, 13, 14 and17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated recombinant protein consisting of the amino acid sequence SEQ.ID.NO:1, and a pharmaceutical composition comprising the isolated protein consisting of the amino acid sequence SEQ.ID.NO: 1 does not reasonably provide enablement for any variant protein , SEQ.ID.NO:1, a pharmaceutical composition

comprising said variants of SEQ.ID.NO:1 and a method for treating or preventing infections comprising said SEQ.ID.NO:1 or variants of SEQ.ID.NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification teaches. lesional psoriasis scales was extracted under acid conditions in the presence of ethanol and concentrated by evaporation. After diafiltration on 0.02 mol/l of sodium phosphate buffer, pH 8 and centrifuging, the supernatant was chromatographed on a bacteria-affinity column (E. coli or S. aureus), which had been produced by coupling heat-inactivated (70°C over one hour) E. coli or Staphylococcus aureus bacteria to an N-hydroxy-succinimide-activated sepharose column (Pharmacia) (I0 x 5 mm). The column was washed first with the equilibration buffer,, and then bonded proteins were eluted with an acid buffer (0.i mol/l of glycine buffer, pH ~3 with 1 mol/l of NaCl) ~ The eluate that contains bonded protein was diafiltered from 0.1% of aqueous trifluoroacetic acid solution and first subjected to a preparative Reversed Phase HPLC separation , SAP-2 was-eluted with 0.8 mol/l of NaCl. A subsequent micro-reversed phase-HPLC analysis with the aid of a C-18 RP column yielded a protein peak that is eluted with 52% acetonitrile, which after SDS-gel electrophorese yielded an individual protein band or two bands corresponding to the mobility of about 20 kD, SEQ.ID.NO:1 Example 1.

The instant inventors believe that the invention relates to making protein variants SEQ.ID.NO:1, (the examiner indicated that protein modifications in claim 1 have been treated as variants) methods for using such protein SEQ.ID.NO:1 or protein variants of SEQ.ID.NO:1 in the prevention and treatment of microbial organisms .

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims as written are drawn to undefined peptides or variants of SEQ ID NO:1 and neither the specification nor the art of record define which amino acid residues of SEQ ID NO:1 are critical for antimicrobial activity in an in vitro screening. As drawn to variants that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in

many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981(1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

Proteins with replacement of a single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins and they differ in native conformation, binding and toxicity, thus exemplifying the importance of structural components to both biological function This information appears to be critical because the art recognizes (see Bowie above) that it is the protein sequence that determines the three dimensional shape of a protein is essential for the binding. Thus, in the absence of guidance in the specification and one could not determine how to make the claimed invention or predict that any particular variant/peptide would function as claimed with a reasonable expectation of success. Neither the art nor the specification as originally filed provides guidance on how to determine which variants of SEQ.ID.NO:1 have

antimicrobial activity that could be used in a pharmaceutical composition. Further , the specification fails to provide guidance how to use the claims SEQ.ID.NO:1 in preventing or treating infections caused by micro-organisms. The specification only provides guidance that the protein , SEQ.ID.NO:1 when incubated with E.coli 50ug/ml and S.aureus 100ug/ml show antimicrobial activity in vitro assays. However, the specification does not provide support for vivo studies against challenge infections for preventing or treating the infections.

The prior art as shown in 102 (a) rejection under paragraph 16 , read on the presently claimed genus SEQ.ID.NO:1 that has structure associated with function. However, the claims also read on wide variety of variants of SEQ.ID.NO:1 , For example: Accession number AF473854; AAL8964 as shown below disclose a variant of SEQ.ID.NO:1 with amino acids substituted but do not appear to have antimicrobial activity. Thus the variant as claimed have no correlation between function and structure, or some combination of such characteristics."

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Qy          1 KPKGMTSSQWFKIQHMQPSPQACNSAMKNINKHTKRCKDLNTFLHEPFSSVAATCQTPKI 60
              ||| |||||||| ||:||||||||||||  |||:|:||||||||||||||||| ||||| |
Db         28 KPKDMTSSQWFKTQHVQPSPQACNSAMSIINKYTERCKDLNTFLHEPFSSVAITCQTPNI 87

Qy         61 ACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCRYKEKRQNKSYVVACKPPQKKDSQQFHLV 120
              ||||  |||||||||:|||| :|||||||||||||  |  |:||| |||: |   : ||
Db         88 ACKNSCKNCHQSHGPMSLTMGELTSGKYPNCRYKEKHLNTPYIVACDPPQQGD-PGYPLV 146

Qy        121 PVHLDRVL 128
              |||||:|:
Db        147 PVHLDKVV 154
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Thus, it appears that there should be a correlation between structure and function of the protein as evidenced by the closest prior art variant. The specification does not provide an adequate support for variants of SEQ ID NO:1 that is required to practice the claimed invention.

The specification provides no guidance or working examples which would provide guidance to one skilled in the art as to which amino acids of the protein , SEQ.ID.NO:1 are critical for the induction of antimicrobial activity and no evidence has been provided which would allow one of skill in the art to predict which of the broadly claimed variants would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Thus, it would not be expected that the claimed variant proteins in the absence of further guidance from the specification, would function as claimed or as contemplated given that there is

no teaching of residues critical to the claimed function. Further one would not know how to use of said variants or protein for preventing or treating infections against challenge infections.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 1-3 ,5, 6, 13 , 14 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by EP943679-A1..

Claims are drawn to a protein /pharmaceutical that as an active mature protein/peptide (protein) has sequences: SEQ ID NO: 1 (Sequence Protocol No. I) (SAP-2); or that as an active mature protein has allelic modifications of one of the amino acid sequences that are mentioned above under a), whereby at least one amino acid of the amino acid sequence is substituted, deleted, or inserted, without in this case significantly affecting the activity of the active protein, or that as an active, mature protein has post-translational modifications of one of the sequences under a) and b), and said modifications do not significantly affect the activity of the active protein, said protein has an antimicrobial and/or antibiotic action,, said protein I, protective groups are arranged at the N-terminus and/or the C-terminus and said protein is a recombinant protein in a pharmaceutical active ingredient in the presence of pharmaceutically compatible and acceptable compounds and vehicles.

EP943679-A1. discloses an Rnase-like protein as shown below which is 100% identical to the claimed protein as in claim1. As this protein has wound healing and anti-viral activity, this protein is active and contains anti-micribial. In the absence of evidence to the contrary this protein protective groups are arranged at the N-terminus and/or the C-terminus with a signal sequence and would have mobility of 6KD under reducing conditions. The art also reads on pharmaceutical composition as the protein in a pharmaceutical active ingredient such as buffer is capable of wound healing or has antimicrobial activity (i.e., anti-viral) and thus can be used for the production of medication. Limitations for treating and preventing etc are considered as the intended use of said composition. The prior art anticipated the claimed invention.

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AAY44192
ID   AAY44192 standard; protein; 156 AA.
XX
AC   AAY44192;
XX
DT   15-FEB-2000  (first entry)
XX
DE   Human keratinocyte-derived RNase-like protein.
XX
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KW   Human; keratinocyte; RNase; angiogenic; antiviral; cytotoxic; cytostatic;
KW   mammal; angiogenesis; wound healing; viral infection; Reoviridae; tumour;
KW   Coronaviridae; Flaviviridae; Picornaviridae; Togaviridae; Rhabdoviridae;
KW   Paramyxoviruses; Bunyaviridae; Orthomyxoviridae; Retroviridae; cancer;
KW   hyperproliferative disorder; diagnosis.
XX
OS   Homo sapiens.
XX
PN   EP943679-A1.
XX
PD   22-SEP-1999.
XX
PF   13-MAR-1998;   98EP-00870053.
XX
PR   13-MAR-1998;   98EP-00870053.
XX
PA   (INNO-) INNOGENETICS NV.
XX
DR   WPI; 1999-510572/43.
DR   N-PSDB; AAZ30692.
XX
PT   New RNase-like protein, useful for treating cancer and promoting
PT   angiogenesis and wound healing.
XX
PS   Claim 4; Page 9; 28pp; English.
XX
CC   This sequence represents the amino acid sequence of a novel human
CC   keratinocyte-derived RNase protein (KRP) which has RNase, angiogenic,
CC   antiviral, cytotoxic or cytostatic activity. KRP may be administered to a
CC   mammal in order to decrease the amount of intracellular or extracellular
CC   RNA or to promote angiogenesis or wound healing. It may also be
CC   administered in order to treat an RNA viral infection caused by
CC   Reoviridae, Coronaviridae, Flaviviridae, Picornaviridae, Togaviridae,
CC   Paramyxoviruses, Rhabdoviridae, Bunyaviridae, Orthomyxoviridae and
CC   Retroviridae. KRP may also be administered to cancer patients to treat
CC   tumours or hyperproliferative disorders. In addition, it may be used to
CC   diagnose cancer and hyperproliferative disorders
XX
SQ   Sequence 156 AA;

  Query Match             100.0%;  Score 711;  DB 2;  Length 156;
  Best Local Similarity   100.0%;  Pred. No. 7.1e-65;
  Matches  128;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 KPKGMTSSQWFKIQHMQPSPQACNSAMKNINKHTKRCKDLNTFLHEPFSSVAATCQTPKI 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         29 KPKGMTSSQWFKIQHMQPSPQACNSAMKNINKHTKRCKDLNTFLHEPFSSVAATCQTPKI 88

Qy         61 ACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCRYKEKRQNKSYVVACKPPQKKDSQQFHLV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         89 ACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCRYKEKRQNKSYVVACKPPQKKDSQQFHLV 148

Qy        121 PVHLDRVL 128
              ||||||||
Db        149 PVHLDRVL 156
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17. No claims are allowed.

Conclusion

18. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600

Padma Baskar Ph.D.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER